DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE PELLETS OF DILTIAZEM HCL

By

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To my father KHAWAJA ABDUL-RAHMAN and

mother MUMTAZ ANWAR

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PEMBANGUNAN DAN PENILAIAN PELET PELEPASAN TERKAWAL DILTIAZEM

ABSTRAK

Satu sistem pelepasan terkawal telah dibangunkan melalui penyalutan satu filem polimer pengawal kadar apa ke atas pelet yang telah disaluti drug, dengan menggunakan diltiazem sebagai drug model. Drug tersebut dilapiskan ke atas pelet lengai dengan menggunakan sistem penyalutan fluidized–bed semburan bawah dan seteruskan disalutkan dengan Eudragit NE40D sahaja atau campuran Eudragit NE40D dengan diltiazem. Kajian pelarutan in-vitro menunjukkan bahawa pelet yang disaluti dengan Eudragit atau campuran serbuk diltiazem dalam Eudragit sebaran berupaya mengekalkan kadar pelepasan sehingga 12 jam. Kajian pelarutan ke atas pelet tersalut juga menunjukkan bahawa kadar pelepasan drug boleh diubah dengan cara yang boleh diramalkan melalui perubahan ke atas tahap penyalutan polimer. Penambahan sebanyak 25% serbuk diltiazem ke dalam sebaran polimer meningkatkan kadar pelepasan drug kerana peningkatan ketelusan filem. Pemasukan 5% metil selulosa atau hidroksipropilmetil selulosa juga meningkatkan kadar pelepasan drug. Tetapi, penggunaan kedua–dua bahan tersebut tidak sesuai kerana pelet–pelet cenderung untuk mengumpal bersama semasa proses penyalutan. Kadar pelepasan drug tidak begitu bergantung kepada pH, kadar agitasi dan kekuatan ionik larutan penampan. Rawatan haba ke atas pelet tersalut adalah perlu untuk memastikan pembentukan filem yang lengkap dan seterusnya pelepasan drug yang tetap selepas tempoh penyimpanan. Kadar pelepasan drug adalah stabil selepas disimpan pada suhu bilik selama 12 bulan. Satu sebaran baru polivinil asetat, Kollicoat SR30D (SR30) juga

telah dikaji sebagai polimer pengawai kadar. Salutan SR30 ke atas pelet yang dilapisi drug mempamerkan kadar pelepasan yang diingini pada pelbagai tahap salutan. Amaun plastisizer seperti propilen glikol atau trietil sitrat dan bahan hidrofobik (magnesium stearat) di dalam formulasi salutan memainkan peranan utama dalam menentukan kadar pelepasan drug daripada pelet tersalut. Kepekatan propilen glikol dan magnesium stearat yang lebih tinggi mempamerkan kadar pelepasan drug in-vitro yang lebih perlahan. Pencampuran pelet tersalut dengan talkum sebelum rawatan pemanasan atau penyimpanan menghapuskan pengumpalan dan kerosakan filem walaupun disimpan pada suhu 60°C. Kadar pelepasan drug daripada pelet tersalut diperlahankan selepas rawatan pemanasan pada suhu yang berapa dan profil pelepasan drug yang stabil dicapai selepas langkah rawatan pemanasan. Kajian mikroskopi skan elektron ke atas pelet memberikan maklumat berguna mengenai integriti filem yang terbentuk. Tiada lapisan salutan drug dan polimer yang jelas dikenalpasti pada magnifikasi yang tinggi. Pelet yang disalut Eudragit telah dipilih untuk kajian bioekuivalen in-vivo yang melibatkan enam sukarelawan sihat dan ia dibandingkan dengan kapsul Herbesser SR. Kedua–dua formulasi adalah setara dari segi tahap biokeperolehan di bawah keadaan berpuasa dan mempunyai sifat pelepasan terkawal yang hampir sama. Kehadiran berbagai puncak di dalam setiap profil kepekatan plasma bagi semua subjek diperhatikan untuk kedua–dua formulasi kajian dan Herbesser SR. Korelasi yang memuaskan juga dipasti di antara data in-vivo dan in-vitro bagi kedua–dua formulasi tersebut. Sebagai tambahan, sifat peralihan gastrousus bagi formulasi kajian dan Herbesser SR dikaji dengan menggunakan pelet paracetamol dan sulfasalazin sebagai drug penanda. Kedua–dua formulasi tidak menunjukkan perbezaan yang signifikan untuk masa pengosongan gastrik dan masa peralihan usus kecil. Bagi kedua–dua formulasi kajian dan rujukan, lebih kurang 14% drug telah diserap apabila pelet–pelet tersebut berada di dalam perut. Semasa berada di dalam usus kecil, amaun drug yang telah diserap daripada formulasi kajian berjumlah lebih kurang 50% and daripada Herbesser SR adalah 37%, manakala di dalam kolon, jumlah yang diserap masing–masing adalah 36% and 49%.

ABSTRACT

A controlled release system was developed from coating drug layered pellets with a release rate controlling polymer film, using diltiazem as the model drug. The drug was layered onto inert pellets using bottom spray fluidized-bed coating system and subsequently coated with Eudragit NE40D alone or in combination with diltiazem. In vitro dissolution studies revealed that pellets coated with Eudragit or the dispersion of diltiazem powder in Eudragit sustained the release rate up to 12 hours. Dissolution studies of coated pellets also indicated that the release rate of the drug could be varied in a predictable manner by varying the coating thickness of polymer. Addition of 25% diltiazem powder with respect to the polymer dispersion enhanced the release rates due to increased film permeability. Inclusion of 5% methyl cellulose or hydroxypropylmethyl cellulose, also increased the rate of drug release, but their utilization seemed to be unsuitable because they tended to cause agglomeration of the pellets during coating. The rate of drug release was reasonably independent of pH, agitation rate and ionic strength of buffers. Thermal treatment of coated pellets was essential to ensure complete film formation and hence constant drug release after different storage time. The rate of drug release was stable after storage at room temperature for 12 months. A new dispersion of polyvinyl acetate, Kollicoat SR30D (SR30) was also investigated as the rate controlling polymer. The coating of SR30 onto diltiazem-layered pellets was found to display desirable release rates at various coating-levels. The amount of plasticizers namely, propylene glycol or triethyl citrate and hydrophobic substance (magnesium stearate) in the coating formulation played a major role in controlling the release rate of drug from the coated pellets. Higher concentration of propylene glycol and magnesium stearate displayed slower rate of drug release in vitro. Blending the coated pellets with talc prior to curing or storage eliminated the agglomeration and film damage even at 60^0C. The rate of drug release was reduced after thermal treatment of coated pellets at 60^0C and invariable drug release profiles were achieved after the curing step. Scanning electron microscopic evaluation of pellets provided useful information on the integrity of the film formed. No distinct coating layer of drug and the polymer was identified at higher magnification. Eudragit-based coated pellets were chosen for in vivo bioequivalence studies involving six healthy human volunteers in comparison with Herbesser SR capsules. The two formulations were comparable in the extent of bioavailability under fasted conditions and possessed almost similar release sustaining behaviour. A slightly faster rate of in vivo absorption was observed with test formulation. The presence of multiple peaks in the individual plasma concentration profiles of all the subjects were common in both test formulation and Herbesser SR. A satisfactory correlation was also established between in vivo and in vitro data for the two formulations. In addition, the gastrointestinal transit behaviour of test formulation and Herbesser SR was monitored using pellets of paracetamol and sulfasalazine as marker drugs. No significant difference was found in gastric emptying as well as small intestine transit times of the two preparations. For both test and reference formulations, approximately 14% of drug was absorbed when the pellets were in stomach. Whilst in the small intestine, the amount absorbed from the test formulation was approximately 50% and from Herbesser SR, was about 37%, whereas in the colon the respective amounts absorbed were 36% and 49%.

CHAPTER 1: INTRODUCTION

1.1 ORAL CONTROLLED RELEASE DOSAGE FORMS

Among the various modes of introducing a drug into the body, the oral route remains the most popular because of its ease of administration and convenience to the patients. Ideally, an oral dosage form should deliver the drug to its site of action, at the optimal rate required to elicit the desired therapeutic response over the duration of the dosing interval. Since blood is usually the medium of transport for the absorbed drug, this ideal is best accomplished by providing a plasma-concentration profile, which produces optimal therapeutic activity. However, this goal can only be partially achieved with conventional dosage forms (Lee and Good, 1987).

Conventional dosage forms such as normal tablets or capsules are generally designed to release their contents immediately for absorption so that the rate and extent of absorption are maximal. Hence, wide fluctuations in peak and trough steady-state drug levels are often obtained with these products in multiple dose administration, particularly if the biological half-life of the drug is short. Such fluctuations are undesirable with drugs of narrow therapeutic indices. Whilst increasing the frequency of dosing may be able to reduce these fluctuations, it may also lead to patient inconvenience and poor compliance. Because of these shortcomings, a number of approaches have been used to formulate sustained release dosage forms. To be effective such formulations must control the rate of oral drug release for absorption over an extended period of time after each administration.

Controlled release dosage forms refer to pharmaceutical preparations that are formulated to deliver therapeutic agents over an extended period in a predictable and reproducible rate after administration of a single dose (Chien, 1992). The terms controlled release, prolonged action, modified release and sustained release are used interchangeably with extended release. An ideal controlled release formulation should release its drug at a constant rate and provides constant drug levels in plasma with reduced fluctuation over a period of 12 to 24 hours such that the duration of its therapeutic effect is sustained. Controlled release technology providing programmable delivery rates has increasingly become more important, especially drugs used for chronic treatment or with narrow therapeutic indices.

1.1.1 VARIOUS APPROACHES FOR ACHIEVING CONTROLLED DRUG DELIVERY

A number of approaches to achieve oral controlled drug delivery has been reported in the literature. These ranged from simple formulation techniques to those using sophisticated technologies. Broadly, the methods can be divided into three main categories, namely those based on a barrier membrane or coat, matrix systems and those using osmotic pressure.

1.1.1 (a) SYSTEM BASED ON BARRIER MEMBRANE/COAT

The German dermatologist Paul G. was the first to use enteric coating for modifying drug release. He reported that if the pills were covered with a thin film of keratin, the pills would not dissolve in gastric acid fluid but in the intestine for absorption (Helfand et al, 1982). Thus, coating the drug particles or pellets with a barrier membrane is an effective means of controlling the drug release. The barrier coat can either be slowly soluble or insoluble in nature. In the former case, the pellets release their contents through erosion of the coat. A typical product utilizing this release mechanism may consist of a capsule containing numerous pellets coated to various thicknesses with some erodible material. Since the rate of erosion of the coat can be expected to be dependent on the coat thickness, such a product will yield a relatively continuous drug release. The Spansule® capsule dosage form marketed by Smith, Kline and French laboratories (SK&F) (US Patent No. 2738303) was based on this design. A variation of this method is to coat the pellets with different coating materials of different dissolution or disintegration times, or successively coating a spherical pellet, in between which, is placed the active drug (Hermelin, 1957). A second mechanism whereby coated pellets release their medicaments is by diffusion of the drug through the intact coat. Following ingestion, moisture within the gastrointestinal (GI) tract penetrates the coat to dissolves the solid drug. The dissolved drug molecules then diffuse through the intact barrier membrane. The rate of drug release can be controlled by varying the nature and/or thickness of the coat or by altering its porosity by incorporating some water-soluble materials into the coat to act as channeling agents. It is interesting to note that osmosis has recently been suggested as an important mechanism for the drug release from such systems (Ozturk et al, 1990; Lindstedt et al, 1989 & 1991).

1.1.1 (b) MATRIX CONTROLLED RELEASE SYSTEMS

A drug with a slow dissolution rate is inherently sustained. For those drugs with rapid dissolution, embedding them within a slowly dissolving or erodible matrix provides a means of retarding the dissolution rate. Most of the oral matrix controlled release products utilize either hydrophilic or hydrophobic matrix systems in which the drug is homogeneously distributed or dissolved in the polymeric matrix. The release of drug occurs mainly through diffusion and erosion. A simple semiempirical equation was introduced in 1985 to describe the drug release behaviour from a hydrophilic matrix system (Peppas, 1985; Ford et al, 1991) while the release from a hydrophobic monolithic matrix system can be adequately described by the Higuchi equation (Higuchi, 1963).

1.1.1 (c) OSMOTIC DRIVEN DEVICES

In an osmotic pump described by Theeuwes in 1975, the delivery of the drug from the system is controlled by the solvent influx across a semipermeable membrane to dissolve the osmotically active drug and / or salt. This leads to an osmotic and hydrostatic pressure differences on both sides of the semipermeable membrane under which the drug solutes are continuously pumped out over a prolonged period of time. OROS® Push-Pull technology based on the above principle was marketed by ALZA Corporation for delivering drugs of very high or low solubility. Such technology provides a zero-order drug release over a 24-hour period. The system consists of two compartments that are compressed into a bilayer core. The top layer contains an active drug and the lower layer contains an osmotically active polymeric agent. The bilayer core is coated with a rigid semipermeable membrane and a delivery orifice is drilled through the coating membrane using a laser beam. The lower layer expands upon influx of water to dissolve the osmotically active salt and the hydrostatic pressure created drives the drug out of the system in the form of a solution or suspension. Thus, the rate of drug release is independent of the drug properties and the release environment. This system has been applied to deliver drug such as nifedipine (Swanson et al, 1987; Chung et al, 1987), metoprolol (Godbillon et al, 1985) and oxprenolol (Bradbrook et al, 1985).

.1.1 (d) OTHER APPROACHES

Other methods used for controlling drug release include ion exchange resins such as, Ionamin capsules manufactured by Penwalt. Ion exchange resins consisted of water insoluble crosslinked polymer with anion or cation groups in repeating positions. Upon administration of a drug-resin complex, the drug would be released through exchange with appropriately charged ons in the GI tract. An improved approach is to coat the ion-exchange system with a hydrophobic rate-limiting polymer such as ethyl cellulose or waxes. In this system, the rate of drug availability can be controlled by manipulating the polymer coat (Grass and Robinson, 990).

Another mechanism for sustaining the delivery of drugs with poor absorption characteristic is o increase its residence time within the stomach. This involves using gastroretentive formulation such as pellets with lower density or pellets that bio-adhere to the stomach to prolong the gastric retention time. Such drug delivery systems also offer a potential for ustained drug therapy for local conditions affecting the stomach.

.1.2 ADVANTAGES AND DISADVANTAGES

Oral controlled release dosage forms are gaining medical acceptance and popularity due to their numerous therapeutic advantages. The therapeutic levels of a drug can be maintained for an xtended period of time, and thus the dosing frequency can be reduced to once or twice daily which in turn leads to increased patient convenience and compliance (Tinkleman et al, 1980). This is of great importance, especially for drugs used in the long-term treatment of chronic iseases. Moreover, controlled release dosage forms are useful for delivering drugs with narrow therapeutic indices since they can reduce the peak-trough fluctuations in blood concentration, being characteristic of multiple dosing using conventional immediate release dosage forms. A better efficacy/toxicity ratio of drug during the entire dosing interval could thus be obtained (Urquhart, 1982). Wide fluctuations in the blood levels may produce high peak drug levels associated with toxicity while low trough levels result in the loss of efficacy. Hence, a better disease management and reliable therapy can be achieved with the controlled release dosage forms (Welling and Dobrinska, 1987).

Elimination of local irritation and erosion arising from exposure of the gastric mucosa to high drug concentrations has also been reported for individual drugs. However, this point remains controversial. Perforations of the small bowel was reported with the OROS controlled release formulation of indomethacin, but it is still unclear whether this was due to local effect of indomethacin, the osmtic agent or a systemic effect related to constant indomethacin plasma levels.

However, controlled release dosage forms also have some disadvantages. The removal of drug from the gastrointestinal (GI) tract is difficult with controlled release preparations if adverse drug effects are observed. Controlled release products may also yield erratic or variable drug absorption due to their increased susceptibility to interactions with the contents of GI tract as well as changes in the GI motility. Moreover, controlled release dosage forms may not be practical for drugs given as large doses (>500 mg) in conventional dosage forms. A controlled release tablet may contain twice the dose of a conventional tablet, and hence the size of the controlled release tablet would become too large to be swallowed easily. Moreover, dose-dumping phenomenon in which large amount of drug is released immediately for absorption into the systemic circulation, may occur leading to potentially toxic levels and adverse drug reactions. The dose dumping is primarily due to a breakdown in the controlled release mechanism, thus the preparation behaves like a conventional immediate release product. In addition, the potential for reduced drug availability due to first pass effect is greater with controlled release formulations than with conventional dosages (Prisant et al, 1992).

1.1.3 MULTIPARTICULATE AND SINGLE UNIT DOSAGE FORMS

Oral controlled release dosage forms can be classified into single and multiparticulate preparations (Bechgaard and Nielsen, 1978). The single unit usually consists of a single tablet such as matrix system while multiparticulate preparation comprises many small subunits like pellets or beads in a hard gelatin capsule. The multiple unit dosage forms offer considerable advantages over matrix tablets. Pellets are usually produced in an ideal spherical shape that is suitable for coating and filling due to their free flowing properties. Multiparticulate system can also provide greater flexibility in terms of dose adjustment, combining two or more compatible or incompatible drugs as well as combining the pellets having different release rates into a single dosage form. The pellets are well distributed in stomach and small intestine after administration and hence minimize the problem of gastric irritation due to reduced local drug concentration as compared to highly localized concentration after the administration of an immediate release dosage form (Wilson and Washington, 1989; Rowe, 1983). There is a rare chance that all pellets in a dose will be disrupted and hence has lesser risk of dose dumping (Beckett, 1985).

Another major advantage is the gradual and to some extent, more predictable emptying of pellets from the stomach with small intra and inter-subject variations. Pellets are usually emptied rapidly from the stomach and can easily pass through the contracted pylorus. On the other hand, gastric emptying of a single unit dosage form is essentially a random process with greater intra and inter-subject variations (Bechgaard, 1982).

1.2 PELLETIZATION

Pelletization process is not only utilized in pharmaceutical industry but also in fertilizer, fish feed and polymer industries. The pharmaceutical industry shows keen interest in this process after the introduction of Spansule® capsule launched by Smith Kline & French. Pelletization can be described as an agglomeration process in which fine powders or granules of drug together with other non-active materials are converted into small spherical and free flowing units which are commonly known as pellets/beads or spheroids. Pellets manufactured in the pharmaceutical industry is normally ranged between 0.5 to 1.5 mm. Pellets can be prepared in different ways such as balling, layering, globulation and compaction (Ghebre-Sellassie, 1989).

Balling process has little application in the pharmaceutical industry but has greater application in the ore and fertilizer industries. In this classical process, finely divided particles are converted to pellets with the addition of appropriate quantities of liquid prior to or during their continuous rolling in drums, discs or mixers (Newitt and Conway-Jones, 1958; Bhrany et al, 1962; Sastry and Fuerstenau, 1977). The dominant stages in this process are nucleation, coalescence and layering. The pellets produced from balling process have a wide particle size distribution due to the random nature of the formation of nuclei (Chambliss, 1989; Wan, 1994).

In layering process, inert nonpareil or preformed drug nuclei are used for the deposition of successive layers of drug in solution, suspension or dry powder. In solution or suspension layering, the drug particles are either dissolved or suspended in binder solution for spraying onto the inert nonpareil. During the spraying and drying stage, liquid bridges that are convertible to solid bridges, are formed and the process is continued until the desired pellet size is achieved. On the other hand, a binder solution is first applied onto the seeds during powder layering, which are then tumbled in the rotating pan containing powdered drug to form layers on the particles until the desired sizes are obtained (Sherrington, 1969; Ghebre-Sellasie et al, 1985).

In comparison, globulation is a process in which hot melts, solutions or suspensions are atomized to produce solid particles through evaporation or cooling and solidification (Sherrington and Oliver, 1981). This process can be sub-divided into two relevant processes of spray drying and spray congealing (Ghebre-Sellasie, 1989). During spray drying, the atomized droplets are evaporated upon contact with hot gas stream whereas in spray congealing, the atomized droplets are cooled to temperature below the melting point of the vehicles.

In pelletization using the compaction process, the drug particles or granules together with or without formulation aids are mechanically forced to produce pellets of definite shape and size (Conine and Hadley, 1970; Carstensen, 1984). Compaction can be divided into compression and extrusion. During compression, the particles undergo either elastic or plastic deformation at high pressure to increase inter-particulate contact. The formulation and processing variables are similar to those employed in the granulation process during tablet manufacturing. In contrast, extrusion is not a single pelletization process but instead is a multistage process. The four main operations involved are preparation of wet mass during granulation, shaping the wet mass into cylindrical extrudates, breaking up the extruded mass and spheronizing it into pellets which are then dried (Conine and Hadley, 1970; Woodruff and Nuessle, 1972).

In addition to the above methods, there are two other techniques of producing pellets, namely cryopelletization and melt spheronization. Both techniques are gaining much interest in the pharmaceutical industry. Cryopelletization is a new freezing technique for conversion of aqueous solutions/suspensions into solid bead-like particles by employing liquid nitrogen as the cooling medium. The pellets are then dried in conventional freeze dryers (Knoch, 1994). This technique was first developed for the nutrition industry as well as for the lyophilization of viscous bacteria. Melt spheronization, on the other hand, is a modified form of balling process and is still in the developing stage. The drug and inactive materials are first converted into molten or semi-molten state, which are then shaped into pellets by using melt pelletizers (Thomsen et al, 1993).

1.2.1 EXTRUSION-SPHERONIZATION

The pelletization process improves dramatically after the introduction of the extruders and spheronizers. At present, two pelletization processes, namely extrusion-spheronization and drug layering are widely used for the production of pellets in the pharmaceutical industry. The equipments used in both processes are discussed below.

1.2.1 (a) EXTRUDERS

There are different types of extruders available and all have the basic principle of forming a wet powder mass through a perforated die or screen to produce cylindrical extrudates. The extruders can be classified according to the die design and feed mechanism for transporting the material to the die. The four main classes of extruders are screw extruder, sieve and basket type, roll (Rowe, 1985) and ram extruders (Benbow and Ovenston, 1968).

The selection of an extruder depends upon the characteristics of the extrudates and the nature of further processing steps required. The ram extruder is usually used during an early experimental stage while a low compaction system such as the screen/screw extruders is appropriate for the production of granules. On the other hand, roll mill is suitable for a dense extrudates that require subsequent spheronization.

Some instrumentation, such as roll extruder with two perforated cylinders, allow the measurement of forces during extrusion. The in-process control could be correlated to the final quality of the pellets (Baert et al, 1992). Harrison et al (1985) measured the force applied on the piston of a ram extruder that is necessary to maintain a fixed extrusion speed.

1.2.1 (b) SPHERONIZERS

Spheronizers consists of a grooved horizontal plate rotated within a stationary vertical cylinder fitted with a door to allow discharge of the spheronized products. During spheronization, the wet extrudes are loaded onto the rotating plate of spheronizer and are transported by centrifugal force to the periphery of the spheronizer. The damp extruded particles or extrudates produced by the extruders described above require further processing to obtain spherical shapes. The extrudates are broken down into shorter and uniform cylinders. The friction plates have two types of grooved surfaces; crosshatch geometry where the grooves form right angles, and radial geometry where a radial pattern is used. During the spheronization process, the extrudates in the form of cylinders undergo different stages to form round pellets. Initially they form cylinders with rounded edges, then dumbbells followed by elliptical particles and finally spheres (Rowe, 1985). A special kind of spheronizer has a lip around the rim of the friction plate, and was claimed to reduce the mixing effect of the friction plate resulting in a smaller amount of fines. In an air-assisted spheronizer, filtered dry air can be passed through the perforated base of the plate to partially remove the surface moisture from the particles. Air also flows through the gap between the plate and the wall. Such specialized spheronizer helps in the movement of the granules/pellets to slide across each other more easily.

1.2.2 COATING TECHNIQUES

Most coating processes utilize three categories of coating equipments, namely conventional pans, perforated coating pans and fluidized bed coaters. However, it should be noted that these coating equipments or processes can also be used to prepare pellets such as layering method mentioned in section 1.3. Fluidized-bed coating technique is best suited for producing modified release coatings especially when dealing with water-based formulations. Three types of spray systems are available, namely top-spray, bottom-spray and tangential-spray systems. However, the latter two systems are usually preferred (Olsen, 1989). The differences in the three systems are summarized below.

1.2.2 (a) TOP-SPRAY SYSTEM

The conventional top-spray system has been used for many years and was originated from the fluidized-bed dryer. In this coating system, the particles are placed in the product container and the particles are accelerated randomly upwards by air where a nozzle sprays the coating material from the top downwards. The spray nozzle is mounted lower than the expansion chamber so that the liquid is sprayed when the particles are moving at a higher velocity. The product then enters the wider expansion chamber resulting in reduction of velocity. The particles then fall back into the container and this cycle is repeated throughout the coating process. Such coating equipments are available in batch sizes between 3 to 1500 Kg.

1.2.2 (b) BOTTOM SPRAY SYSTEM

Bottom spray system or more commonly known as Wurster system is widely used for coating and layering of pellets as small as 100 microns. At the base of the coating chamber, there is a fine screen and an air distribution plate while in the center of the plate, a nozzle is fixed to spray coating formulation through a cylindrical partition. The air distribution plate is designed to generate a circulatory motion of particles. The fluidized particles move upward through the spray zone and enter the expansion chamber where they defluidize and fall outside the partition known as downbed. The downbed region is a slightly expanded bed where the air rate is below the minimum fluidization velocity and in this region sticking is more likely to occur. The cycle completes when horizontal transport of the product into the spray zone occurs through the small gap at the base of the partition. The presence of the partition in the Wurster chamber produces more organized movement of particles, which is less affected by bed load. The Wurster-based coating process is a complex process with many interrelated processes (Christensen and

Bertelsen, 1997). Proper selection of the distance between the base of the partition and the air distribution, which is known as the partition height results in a rapid and smooth movement of particles through the spray zone.

1.2.2 (c) TANGENTIAL SPRAY SYSTEM

In this system, the product container consists of cylindrical chamber with a variable speed disk at its base. A gap exists at the perimeter of the disk through which the process air is drawn. Three forces act on the product during processing. Centrifugal force due to disk spinning makes the product to move forward and outward toward the chamber wall. The fluidization air produce acceleration upward and gravity makes the product to tumble toward the disk surface once again. The spray nozzle is fixed tangentially and sprays on the tumbling product in the bed. Coatings can be applied using water, organic solvents or via hot melts. The fluidization pattern is quite different with the product flowing in a reverse direction as compared to that in the top spray and bottom spray systems. Tangential spray process is the most stressful mechanical method, where the pellets are randomly fluidized and their movement is related to size and density. The high speeds employed result in the loss of the rope-like motion of the pellets and cause the bed to slide on the rotating disk as the liquid is sprayed. Lower disk speeds also cause similar problems due to uneven distribution of the spray (Vuppala et al, 1997).

It has been observed that the quality of the modified release films is related to the type of equipments selected in the following order (Mehta and Jones, 1985):

Wurster = Tangential spray > Side vented pan >> Conventional pan

The Wurster and Tangential spray give the best drying characteristics due to the small distance between the spray nozzle and the particles which helps to control deposition of the coating material and maximize the quality of the final coating. In the Wurster technique, the movements of particles and spray droplets are co-current and therefore, have many chances to come into contact. On the other hand, the fluidizing air and spraying are counter current in the top-spray method. Therefore, it is conceived that the spray is more gentle and homogeneous in Wurster technique while top-spray method causes an excessive spreading on the particles.

1.2.3 COATING POLYMERS

Controlled release coatings began as organic solutions and evolved to aqueous dispersions in response to environmental regulations and safety. An early and widely known aqueous product was the pseudolatex that consisted of a finely divided colloidal dispersion of water insoluble polymer in the aqueous media. The other polymeric dispersions are latexes prepared by emulsion polymerization of monomer and dispersions of micronized polymeric powder. Some aqueous coating systems have been described to possess pH-dependent properties, but most are unaffected by the pH of the dissolution media. Several aqueous polymeric dispersions require the presence of plasticizer to facilitate film formation. A number of aqueous dispersions are plasticized during the manufacturing stage while others require the addition of an appropriate amount before the coating process.

The United States Pharmacopeia (2000) lists three sustained release coating materials, namely cellulose acetate, ethylcellulose and methacrylic acid copolymers that could function as rate controlling membranes. Polymeric dispersions available commercially are listed below:

Brand Type	Polymer Component	Additives
Eudragit L30D	Copoly (MA-EA)	Tween 80 (2.1%), SDS (0.9%)
Eudragit RS/RL 30D	Copoly (EA-MMA-TAMCl)	Sorbic acid
Eudragit NE30D	Copoly (EA-MMA)	PNP
Kollicoat EMM30D	Copoly (EA-MMA)	Nonoxynol100 (1.5%)
Kollicoat SR30D	Polyvinyl acetate	Povidone (2.5%), SDS (0.3%)
Aquacoat/Surelease	Ethyl cellulose	Cetyl alcohol (9%), SDS (4%)/ Dibutylsebacate, Oleic acid, Ammonia fumed silica.

MA, Methacrylic acid; EA, Ethyl acrylate; MMA, Methyl methacrylate;

TAMCl, Trimethylammonioethyl methcrylate chloride; SDS, Sodium lauryl sulphate and

PNP, Polyoxyethlene nonyl phenyl ether.

Eudragit L30D is a copolymer of ethyl acrylate with methacrylic in ratio of 1:1 and has been used as an enteric coating material.

Eudragit RS30D and RL30D (RL30 & RS30) are copolymers of ethyl acrylate and methyl methacrylate with trimethyl ammonioethyl methacrylate chloride as a hydrophilic group in ratios of 1:2:0.1 and 1:2:0.2 respectively. Both are available as 30% w/v colloidal dispersion, stabilized in water by the positively charged quaternary ammonium. The release of drug can be controlled by mixing RL30 and RS30 in different ratios.

Eudragit NE30D (NE30) is a copolymer of ethyl acrylate and methyl methacrylate in a ratio of 2:1. It has a lower softening temperature as compared to RL30 and RS30. NE30 forms flexible and expandable films while RL30 and RS30 form hard films under room temperature. Kollicoat EMM30D is a different trademark but having similar polymer composition and properties as that of NE30. The difference in the two brands lies in the selection of additives used in their preparations. The permeability of these films and hence the drug release from the coated pellets are pH independent.

Kollicoat SR30D is polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulfate. It forms hard, colorless or faint yellowish film in the absence of a plasticizer.

Cellulose derivatives cannot be formulated directly in latexes and are prepared as micronized powder. Film formation is easier from dispersions of micronized polymeric powders of small particle size as compared to large particle size. The effect of particle size on film formation was reported by Nakagami et al, (1991). They found that micronized ethyl cellulose with large particle size formed poor film and required more plasticizer to form a continuous film.

1.2.3 (a) ADDITIVES USED FOR AQUEOUS BASED POLYMERS

Plasticizers are incorporated for certain polymer coatings to reduce the film formation temperature as well as the glass transition temperature. Generally, the main function of a plasticizer is to increase the film flexibility. Plasticizers also have a significant effect on drug release when they are incorporated in the rate controlling membranes for coating. The inclusion of a suitable plasticizer prevents the cracking of polymeric coat and improves the drug release retardant properties of the coat (Rowe, 1986).

Hydrophilic materials such as polyethylene glycol, methylcellulose, hydroxypropylmethyl cellulose (HPMC), polyvinylpyrrolidone and glycerine are usually added into water insoluble dispersions to modify the permeability of the coats formed and hence the drug release profiles. The addition of HPMC to a water insoluble membrane was reported to cause pore formation resulting in a faster drug release (Govender et al, 1995). On the other hand, talc, magnesium stearate and silica are used to reduce the stickiness of the coating formulations (Ghebre-Sellassie et al, 1986 & 1987). Pigments like titanium dioxide are widely used in coloured film coating.

1.2.3 (b) MECHANISM OF FILM FORMATION

Film formation from a latex or pseudolatex takes place when droplets of the polymeric dispersion are deposited on the particles. This is followed by the evaporation of water and coalescence of the polymer particles into a continuous film. The formation of film coatings from aqueous polymer dispersions is a complex process, which is highly dependent on additives and processing parameters. For example, coating in a fluidized bed at the minimum film forming temperature may lead to incomplete film formation (Lippold and Monells, 2001). It was also found that the difference in the drug release behaviour of aqueous-based and organic solution-based coatings of ethylcellulose was attributed to the difference in the film formation process (Wesseling and Bodmeier, 1999). Guo et al, (1993) suggested that film formation from the aqueous latex dispersion proceeded gradually from the top to the bottom of the film. Various theories have been presented to describe the mechanism of film formation from aqueous polymeric dispersions (Fukumori et al, 1991; Lehmann, 1989; Muroi, 1970; Steuernagel, 1989). Fusion and film formation of polymeric particles can be explained by the wet sintering theory for particles suspended in water, the capillary pressure theory for particle layers in water at various degrees of saturation, and the dry sintering theory for dry particles layers (Fukumori, 1994).

1.3 EVALUATION OF CONTROLLED RELEASE PRODUCTS

1.3.1 IN-VITRO EVALUATION

In-vitro dissolution study is useful in the initial stages of development and evaluation of controlled release dosage forms. It also provides useful information regarding the factors that could affect the drug release behaviour of controlled release preparations, which include processing variables, lot to lot uniformity as well as alterations in formulation or manufacturing site and stability determinations during various stages of the development process.

However, it is not possible to include all the variables in the in-vitro test design that can affect the in vivo dissolution in the GI tract. As far as possible, the in-vitro test conditions should have meaningful relationships to the conditions in GI tract and should be the part of dissolution test methodology (Smollen and Ball, 1984). Choice of dissolution test conditions should be based whether the drug is to be dosed in the fed or fasted state.

Various dissolution-testing devices have been developed and reviewed (Banaker, 1991). Generally, two dissolution systems can be distinguished, namely those based on stirred vessels and those based on flow through cells (Nelson and Muller, 1979). The former systems contain large volume of dissolution medium maintained at 37^0C in a round flask that is mechanically stirred with a cylindrical basket or paddle. The later systems consist of a small dissolution cell holding the dosage form through which fresh solvent circulates at a constant rate without any agitation. The official in-vitro dissolution methods in the USP 24 for testing oral controlled release dosage forms are rotating basket, paddle method, reciprocating cylinders, and flow through cell. Alternative unofficial in-vitro methods include the flow through dissolution method, rotating bottle or flask methods, intrinsic dissolution method and peristalsis method (Shargel and Andrew, 1999). Nevertheless, the rotating basket and paddle methods are still commonly used to evaluate the dissolution characteristics of sustained release products. The in vitro dissolution method should be reproducible and at the same time, discriminative enough to detect inferior batches of similar products. Moreover, the sampling times should span from the first hour until at least 75% of drug has been released in order to detect any dose dumping phenomenon and to ensure a complete release of drug. It is imperative that the in vitro dissolution method should reflect the conditions in the GI tract. However, this may not always be possible due to the changing environment along the GI tract as well as alteration during different food status.

The dissolution media in the small intestine is a complex mixture of bile salts, lecithin, cholesterol and a wide range of lipid materials that can vary considerably with meal type and diet, being different from the conditions in the stomach. Nevertheless, in vivo solubilization can be partially simulated by the addition of surfactants into the dissolution medium to maintain sink condition, such that the drug completely dissolves in less than 20-30% of the dissolution medium. Other important factors that should be considered in the dissolution tests are the types of dissolution apparatus, size and shape of dissolution vessels, volume of medium and mixing or circulation of the dissolution medium and the duration of the test.

Pellet coated with a polymeric membrane provide a certain amount of resistance to drug diffusion from the drug reservoir to the surrounding medium. The driving force of such systems is the concentration gradient of drug molecules between the reservoir and the medium. The drug entity from film-coated dosage forms may be transported through a hydrated swollen film, via a network of capillaries filled with the dissolution media or driven by an osmotic pressure difference between the core content and the surrounding dissolution media. Base on Fick's first law of diffusion, the release rate of a drug from a reservoir coated with polymeric system at steady state is expressed as follows:

$$\text{Release rate} = DKA\Delta C / L \qquad (1.1)$$

Where D is the diffusion coefficient of the drug, K is the partition coefficient of drug between the polymeric barrier and aqueous phases, A, the surface area, ΔC, the concentration gradient and L, the thickness of the film. In the case, when all the terms are held constant, the amount of drug release as a function of time can be obtained on the basis of zero order kinetics.

$$\text{Release rate} = K \qquad (1.2)$$

Where K is the release rate constant. The drug layer of coated pellets must continually release sufficient drug to maintain a constant concentration gradient across the rate-controlling membrane for sustaining zero order release rates. However, when the solid drug has been depleted, the drug release will follow first order kinetics, the rate being dependent on the drug concentration remaining in the reservoir.

1.3.2 IN VIVO EVALUTION

Due to the difficulty of in vitro dissolution studies to simulate the actual environment and conditions in vivo, in vivo performance of a controlled release dosage form is best evaluated using human subjects. However, this will increase the cost of product development. In the absence of in-vivo testing, it is generally impossible to make any decision about bioavailability from the dissolution data alone. It has been emphasized that bioavailability testing in human subjects provides the most authentic means for the validation of the final product. A comparison of drug blood levels of the test product with that of a reference product containing the same drug can be achieved by administering the drug solution orally or intravenously, or a proven conventional or controlled release preparation. The bioavailability of the test product can then be estimated from the analysis of pharmacokinetic data. A single dose bioavailability is usually sufficient but some regulatory agencies like Food & Drug Administration (FDA) may require multiple dose steady state studies for registration of the product (Skelly, 1986; USP 24, 2000). Moreover, the effects of food also require to be evaluated.

Over the last two decades, attempts were made to establish a correlation between percentages of drug absorbed in-vivo with percentage of drug dissolved in-vitro at different time intervals. In an acceptable in-vitro and in-vivo (IVIV) correlation, a linear relationship should be established between these parameters. There are reports that indicate satisfactory IVIV correlation could be established for various dosage forms (Yuen, 1991; Peh and Yuen, 1996). Nevertheless, an IVIV correlation is more relevant for controlled release dosage forms as compared to immediate release preparations because the rate-limiting step in the absorption process for the former is the drug release rate.

A bioavailability study alone may not be sufficient for optimization of a new controlled release formulation because it does not allow to prediction of physiological variables such as gastric emptying and intestinal transit behaviour (Digenis, 1982; Davis, 1983). Therefore, in-vivo visualization and transit behavior of oral dosage forms within the GI tract has become an important tool for the development of controlled release formulations (Wilson & Washington, 1988).

1.4 GASTROINTESTINAL TRANSIT BEHAVIOUR OF CONTROLLED RELEASE DOSAGE FORMS

Drugs that are administered orally will pass through various regions of the GI tract such as stomach, small intestine and large intestine. The biological environment and absorptive capacities are quite different among these regions and these differences can give rise to variations in the bioavailability of drug from the stomach, the small intestine and the colon. The small intestine has the greatest absorptive surface area due to the presence of villi and microvilli and therefore, most drugs are mainly absorbed from this part of the GI tract. Thus, the biological availability of a drug from an oral dosage form can be affected by its length of residence time in the stomach and small intestine. The stomach is able to empty different materials at different rates even though they might have been taken simultaneously. Fluids and small particles are emptied from the stomach more rapidly than solids, which are pushed back to some extent at the pylorus until they have been reduced in size small enough to pass through the pyloric sphincter.

A solid dosage form administered to a fasted stomach or following a light meal may be emptied rapidly from the stomach and pass quickly through the small intestine to the colon (Hunter et al, 1981). A special mechanism known as the interdigestive myoelectric complex (IMC) or housekeeper wave can produce powerful contractions in the GI tract that will sweep indigestible material from an empty stomach past the pylorus into the duodenum. Latter waves will move the material rapidly down the small intestine into the colon.

In general, the presence of food in the stomach increases the gastric emptying time and thus can delay the absorption of drug in the small intestine. However, the gastric emptying rates of multiparticulate dosage forms are not severely affected by the presence of food. The emptying of the pellets can be prolonged by the heavier meal, but not to a similar extent as the single large unit. When pellets are administered with a meal, they tend to empty in a similar pattern as digestible component of the meal.

Gastric emptying time of single non-disintegrating tablets having diameter 10-16 mm range from 0.5 to 4.5 hours whereas granules or pellets are emptied gradually from the stomach with a mean time of 1.5 hours (Bechgaard and Christensen, 1982). The gastric emptying of encapsulated pellets depends upon the nature of the capsule, the speed at which it disintegrates and the degree of dispersion of the pellets in the gastric contents.

Unlike gastric emptying, small intestinal transit of a dosage form is unaffected by their physical state as well as the presence or absence of food, although high calorific loads may slow it slightly (Davis et al, 1987). A review of the literature suggests that small intestinal transit time